

# **Free Factories: from the Quantum Coreworld to the Personal Genome Project**

**(a tour of Genomics, Computing and Economics topics in my research)**



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# Overview

 “Big Data” and Free Factories

## **Applications of Free Factories:**

Swift, Editing, Four Individual Genomes

## **The Aim of Free Factories:**

Enable the Personal Genome Project to bring together physicians, scientists and the general public in a single endeavor

# **Nucleic acids are the largest repository of digital information on Earth**

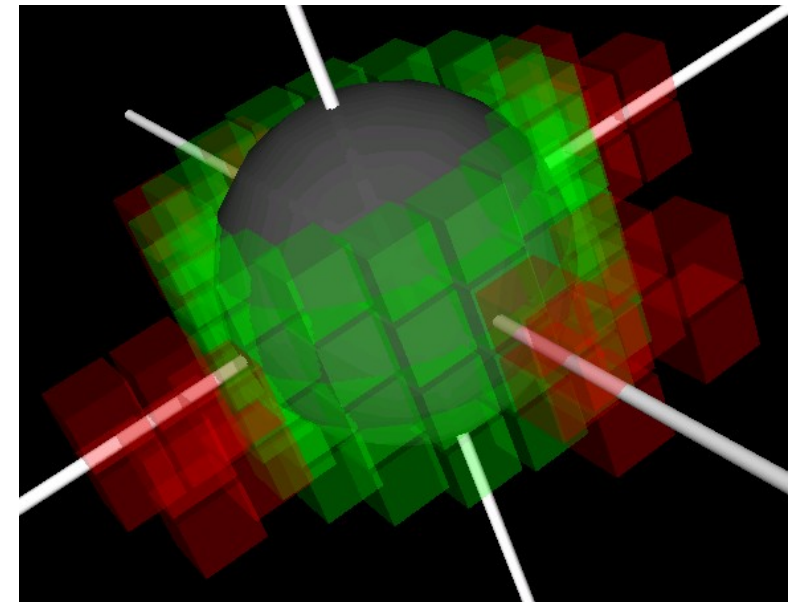
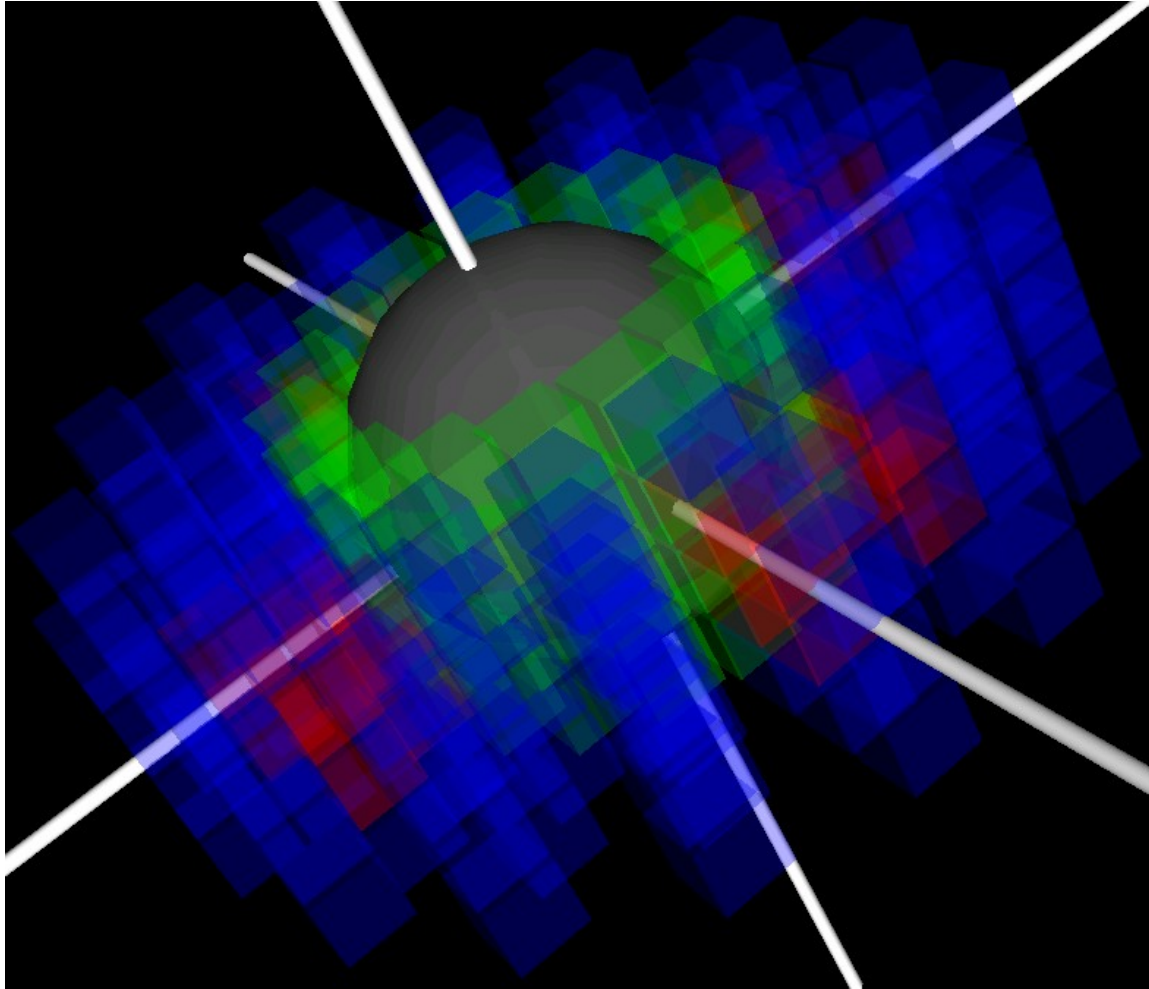
**NCBI Trace Archive -  $10^{15}$**

**“Ordinary” digital universe -  $10^{21}$**

**Human associated digital universe -  $10^{32}$**

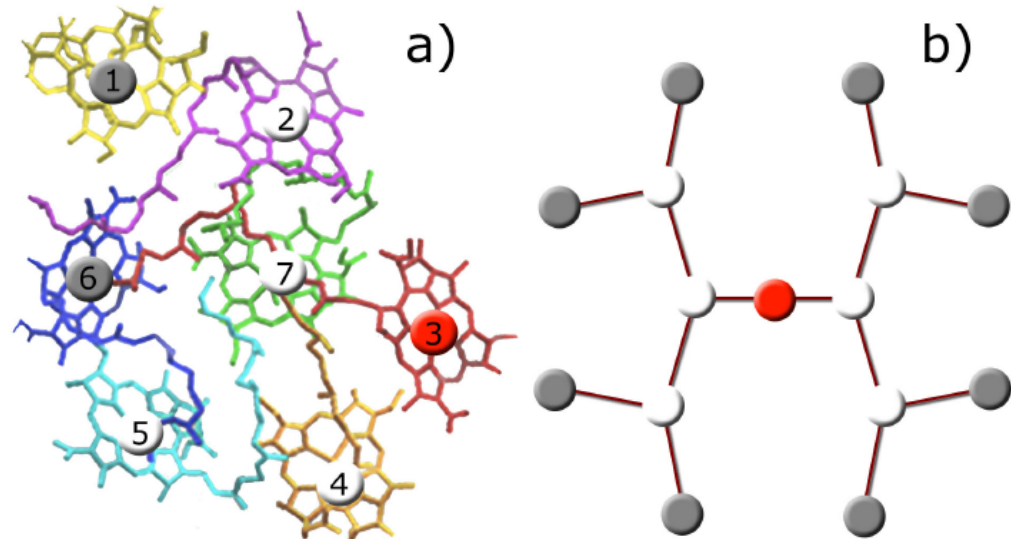
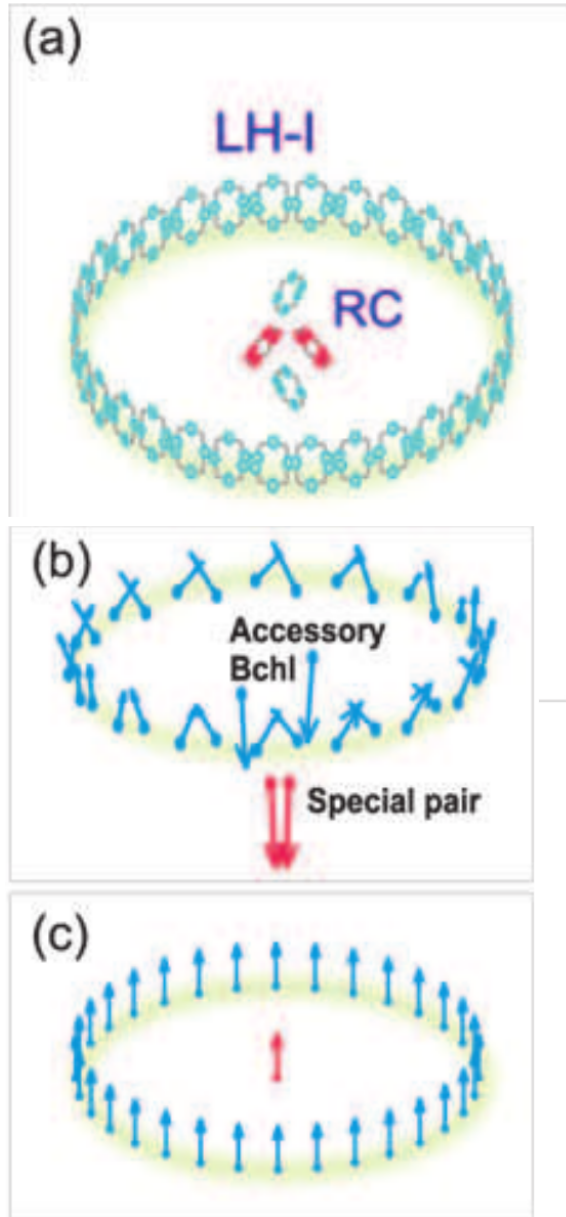
**Biological digital universe -  $10^{36}$**

# **The Quantum Coreworld is a 3D digital evolution system consistent with the rules of quantum information processing**



Translucent cubes represent one femtoliter of water (a cube one micron on each side)  
Digital organisms—written in a simple assembly language—evolve in the Coreworld  
Regions of the world periodically exchange material at well defined boundaries (red)  
New digital lifeforms enter the world nearest to the center (green)

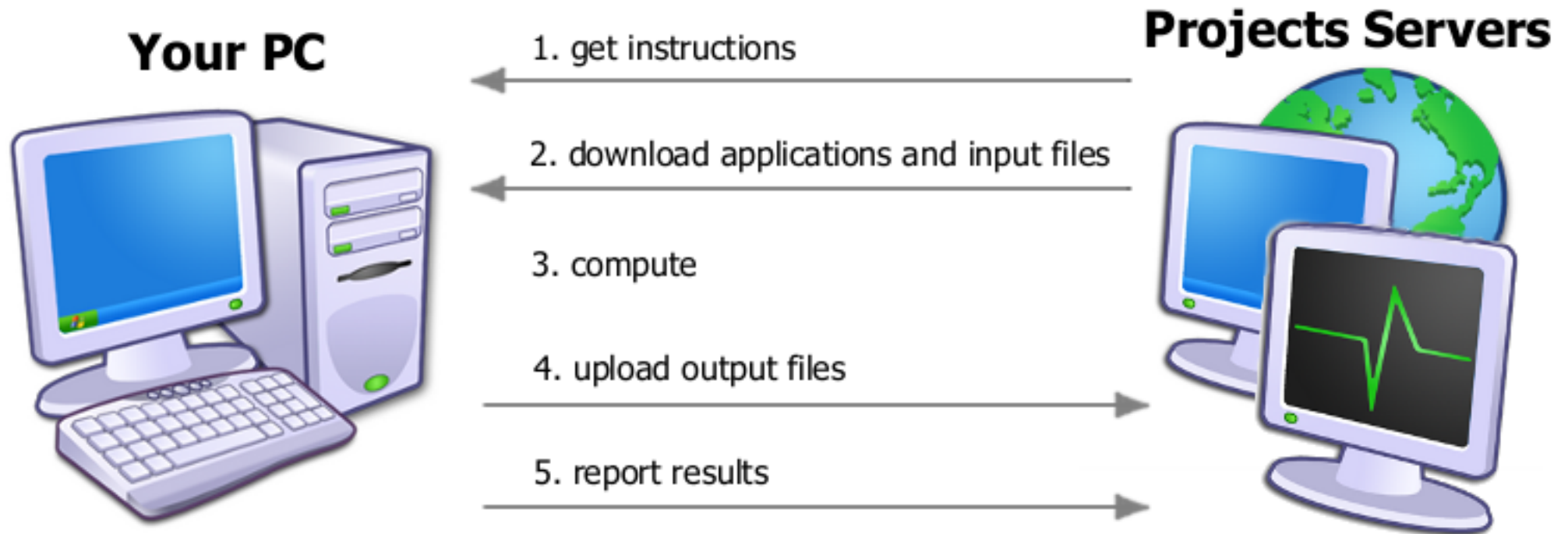
# Quantum Information in Real Biology



ArXiv:0807.0929v1—Aspuru-Guzik group (Harvard)

Schematic of the LH1-RC core of purple bacteria *Rhodobacter sphaeroides*. Olaya-Castro (2007) Phys Rev B.

# Volunteer Computing



**Active: 335,473 volunteers, 562,937 computers.  
24-hour average: 1,309.43 TeraFLOPS.**

<http://openwetware.org/wiki/PersonalGenomes@Home>

# **A Free Factory is inspired by Free Software**

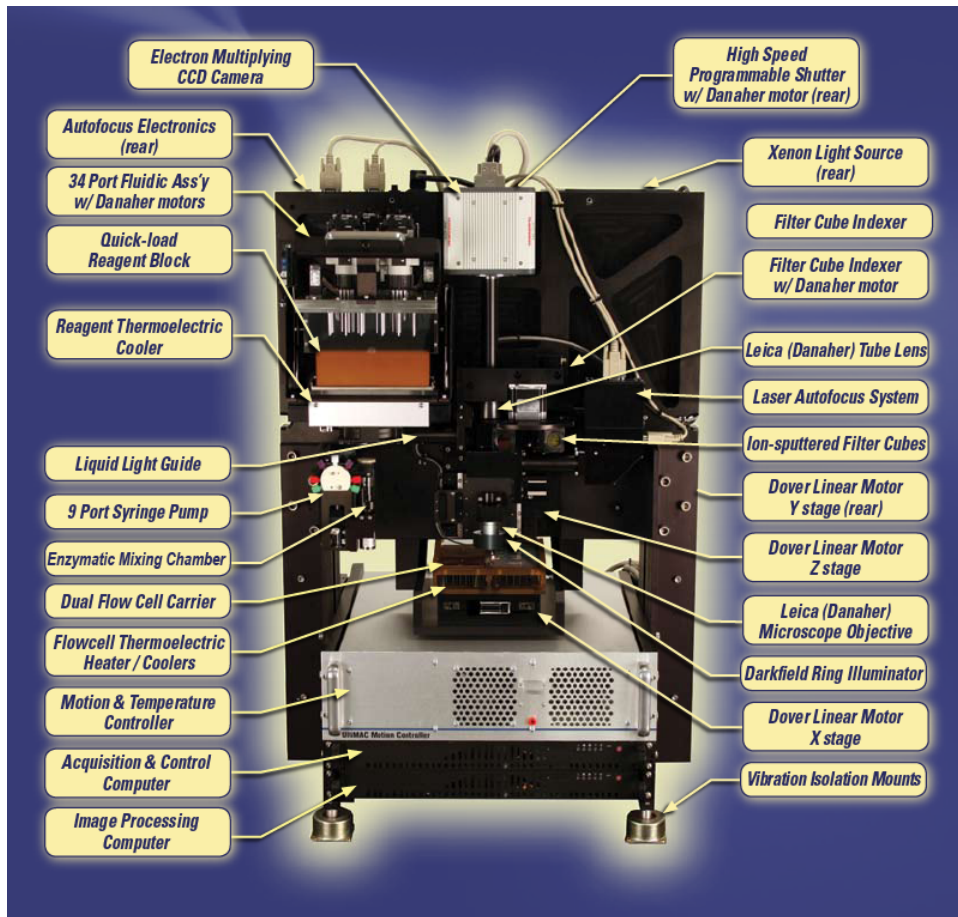
**Free Software** is a matter of the users' freedom to run, copy, distribute, study, change and improve the software.

(<http://www.gnu.org/philosophy/free-sw.html>)

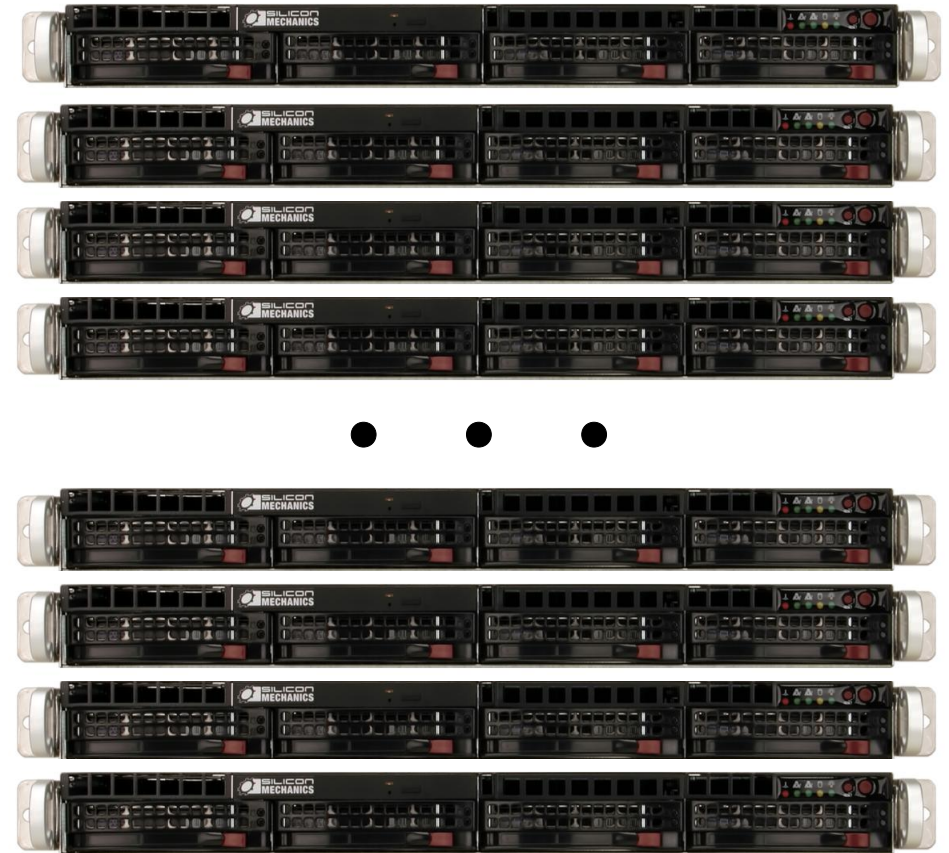
**A Free Factory** should protect the freedom of its user community to:

- 1) operate their own identical factory;
- 2) operate a modified factory;
- 3) distribute the information required to operate and modify the factory to others, and;
- 4) study and improve all factory equipment, methods, software, raw materials, and so on.

# A Free DNA Sequencing Factory could be built by combining the “Polonator” with commodity computers running Free and Open Source Software



Courtesy — Rich Terry and Greg Porreca



I designed the Free Factories computational infrastructure to complement the Polonator.

With sequencing costs falling more rapidly than computing costs, this is a formidable challenge.

# **A recent budget for a Free (DNA Sequencing) Factory**

Setup costs (\$490,000 total)

- \$150,000 - Polonator
- \$80,000 - local storage & computation cluster
- \$160,000 - remote storage & computation cluster (deployed in second year)
- \$100,000 - cluster maintenance, support, training (2 years, 1/2 FTE)

Operational costs (\$181,000 in first year)

- \$30,000 - power, cooling, network for Polonator and local cluster
- \$40,000 - bioinformatics technician (1/2 FTE)
- \$40,000 - lab technician (1/2 FTE)
- \$71,000 - reagents (\$7,085 per run, w/ 2x13bp reads, 100Gbp)

Operational costs (\$315,000 in second year)

- \$30,000 - power, cooling, network for Polonator and local cluster
- \$30,000 - power, cooling, network for remote cluster
- \$80,000 - bioinformatics technician (1 FTE)
- \$80,000 - lab technician (1 FTE)
- \$95,000 - reagents (\$4,769 per run, w/ 2x48bp reads, 740Gbp)

**Total costs (\$986,000 two years w/ 840Gbp at \$1174 per gigabase.)**

**In this budget, computing costs are 38% of the total while they were only 11% for a similar project last year.**

To realize the benefits of cheap sequencing, free and open source methodologies help us consider the whole ecosystem of scientists, physicians and the general public as a single system.

# Overview

“Big Data” and Free Factories

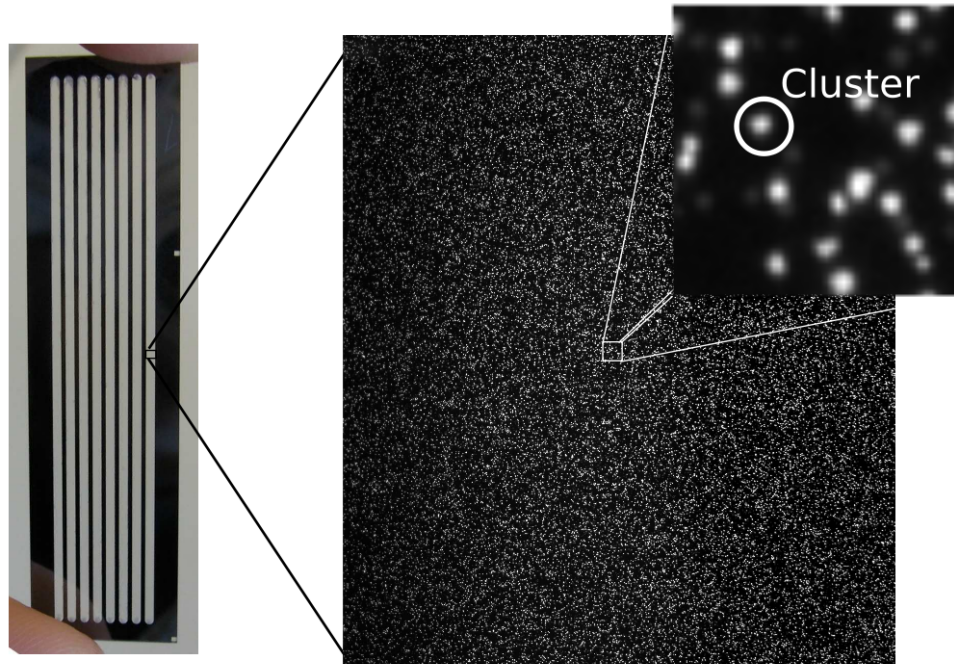
## **Applications of Free Factories:**

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# Swift—the open source data processing pipeline for the Illumina GA achieves a 14% improvement in placed reads for PGP2 data

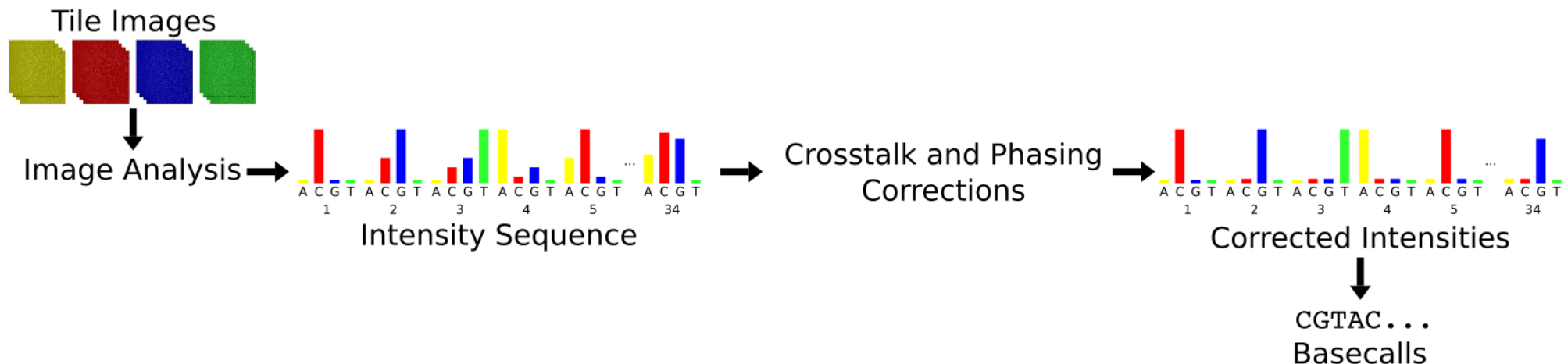


An Illumina GA2 flow-cell consists of 8 lanes which are imaged in 100 tiles (see left)

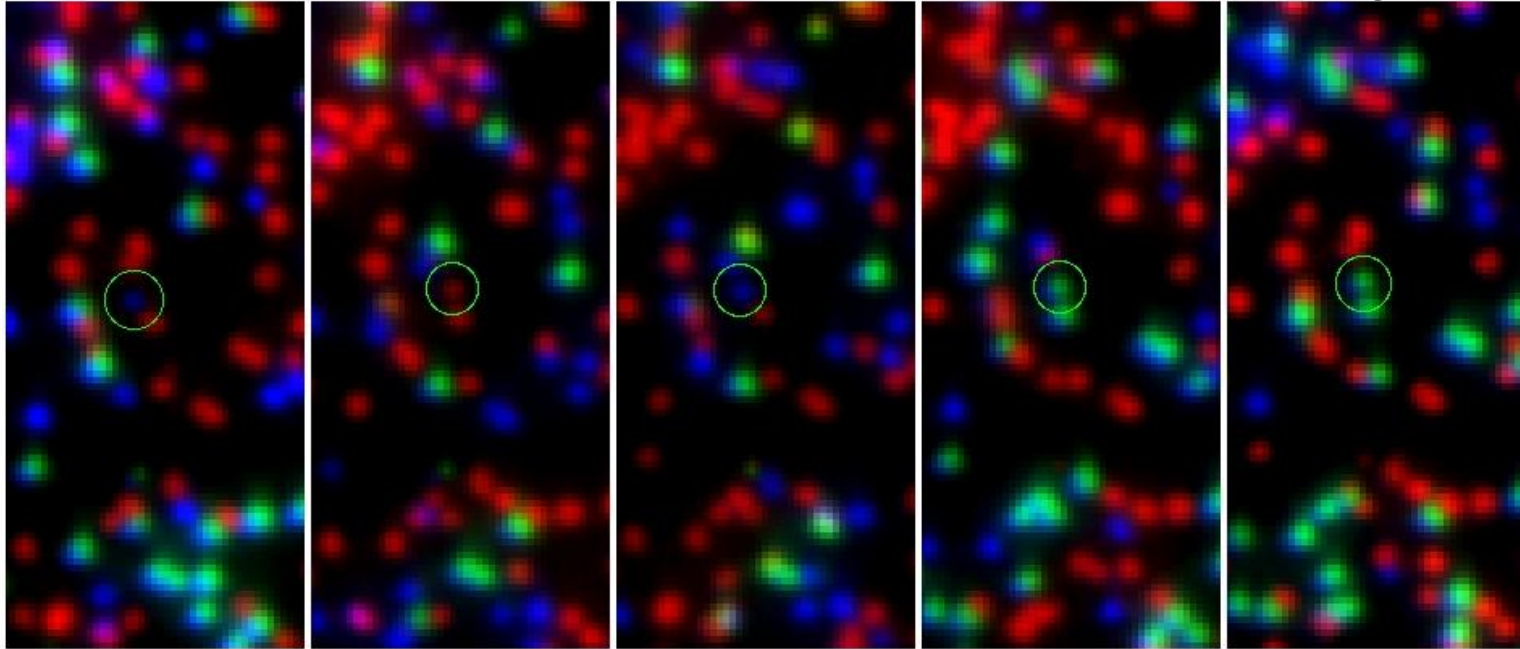
The Swift pipeline examines all images in a tile and makes basecalls. (see below)

This process is very similar for the Polonator and for ABI SOLiD

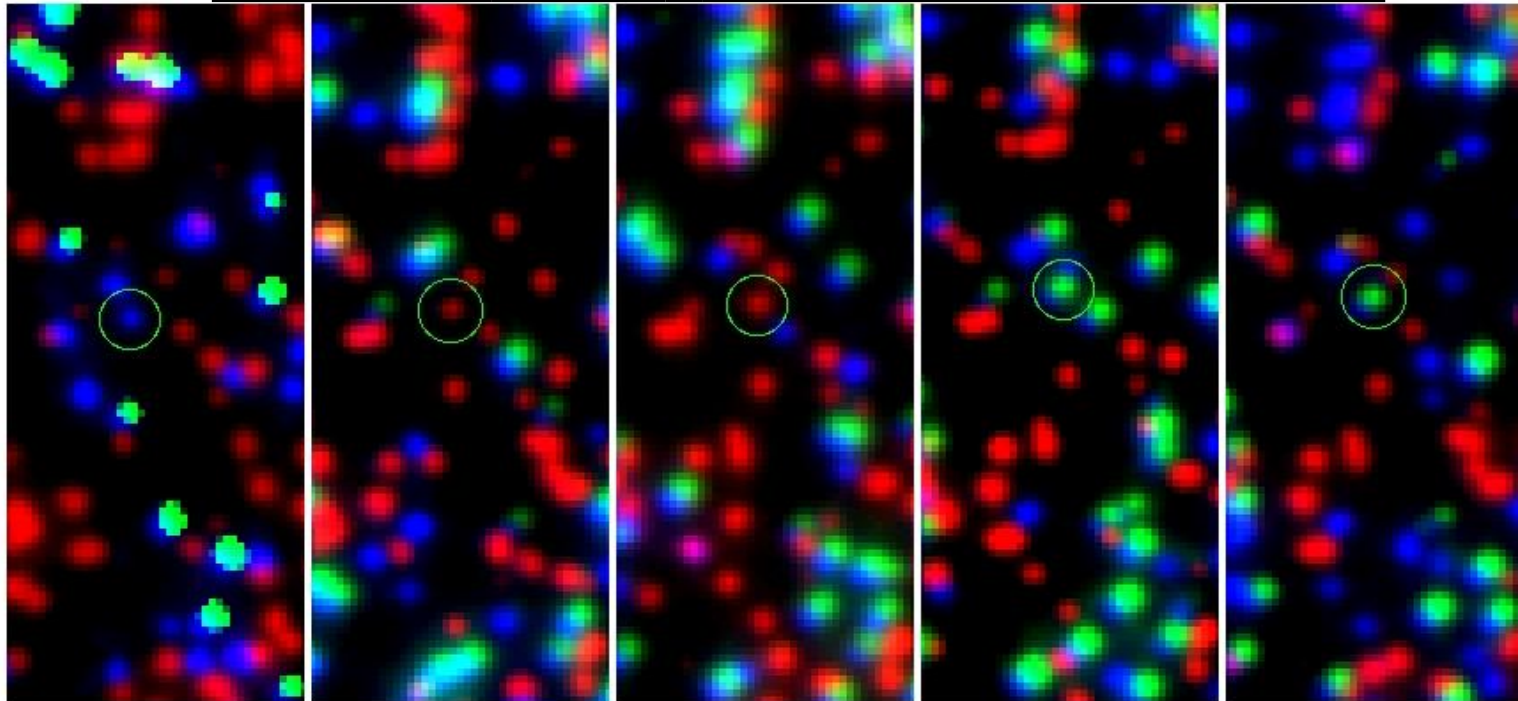
The community is eager to adapt the pipeline to new instruments



GCACACGGTCTGGGCCAAGCAGATTGCAGAGGGCGGg



CAGCACACGGTCCGGGCCAAGCAGATTGCAGAGGGCG



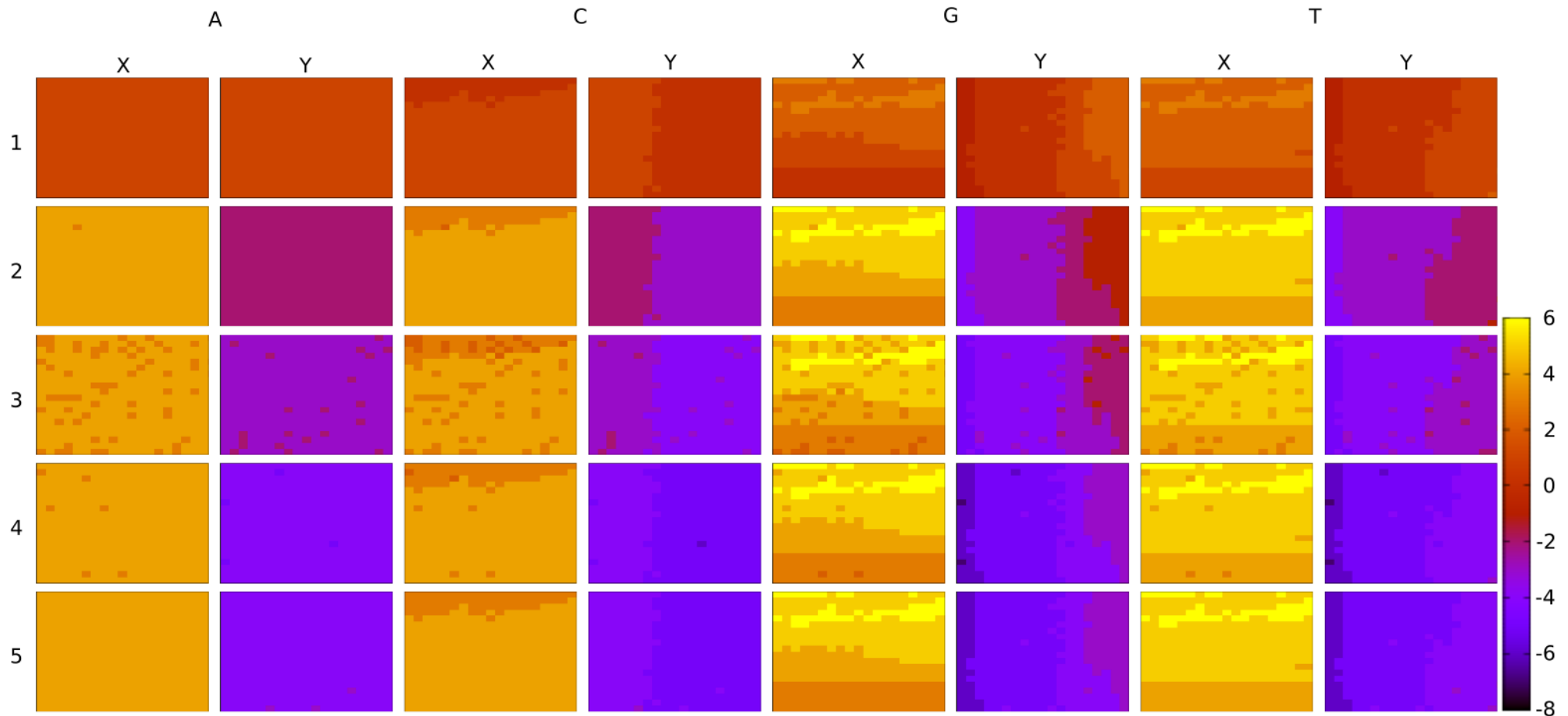
Red = C

Green = G

Blue = T

Courtesy – Andrea Loehr

# Open-source encourages innovations on one platform to be adopted on others



Plot shows X,Y offsets—separately for A,C,G,T florescence channels—in 400 subregions from 5 tiles of Illumina data (processed by the Swift pipeline). The Swift community is eager to try such innovations in the Polonator.

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“Big Data” and Free Factories

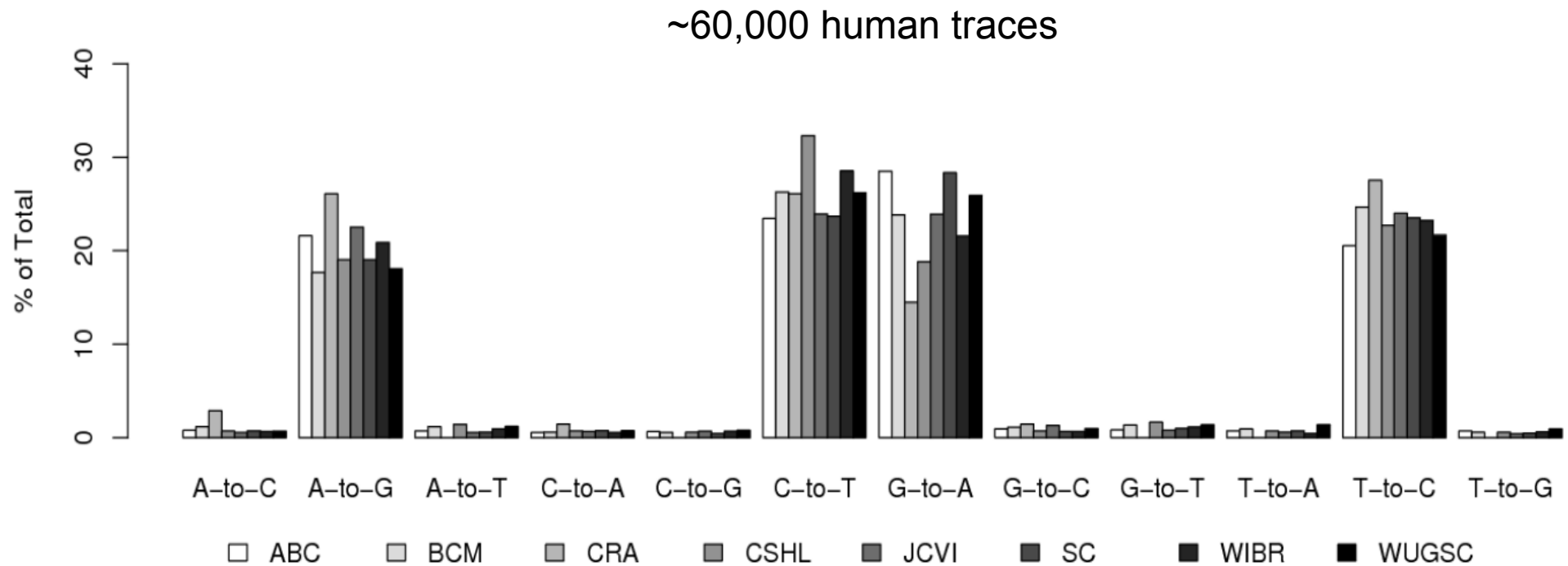
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# Search for DNA and RNA editing candidates



**Align 600 million traces (200 million human) to their reference genome**

**Extract 20.7 million w/ three consecutive mismatches**

**Report mismatches with phred 40 or greater and spanning 100bp or more**

**Consumed 5.8 terabytes of disk and 5 years of computer time**

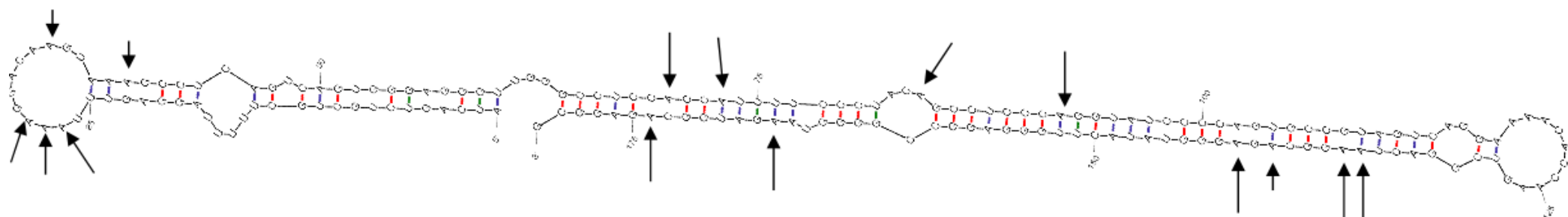
Genome	421	CGGTCCTGAAGGCACAAGTAAGTTACATGAGGAAGTGGCTCAAGTGCCCATGGTCTCTAC	480
Trace	421	.....	480
Genome	481	TCCTGCCACCTGCCTTCTCTCCCCTAGCCTGCACCGATGGCCTCATGGGGAGTTCCTGT	540
Trace	481	.....	540
Genome	541	GATCAGTTGACAGAGGAAGGGAAGACTAGGCCCTGGTTCAGAGATGGTTCTACATGATAT	600
Trace	541	.....	600
Genome	601	GCAGGCACCACCCGGAAGTGGACAGCTGCAGGACTACAGCCCTTTCTAGGACATCCCTGA	660
Trace	601	..... <b>A</b> ..... <b>A</b> .....	660
Genome	661	AGGACAGCGGTGGAGGGAACCTCCAGTGGGCAGAACTTCGAGCAGTGCACCTGGTTATG	720
Trace	661	..... <b>AA</b> .....	720
Genome	721	CACTTTGCATGGAAGGAGAAATGGCCAGATGTCTGATTATATACTGATTCATGGGCTGCA	780
Trace	721	..... <b>A</b> .....	780
Genome	781	GCCAATGGTTTGGCTGGATGGTCAGGGACTTGGAAGAAGCATGATTGGAAAATGTGTGAC	840
Trace	781	..... <b>A</b> ..... <b>A</b> ..... <b>A</b> ..... <b>AA</b> ..... <b>A</b> ..	840
Genome	841	AAAGAAATCTAGGGAAGAAGTATGTGGATGGACCTCTCTGAGAGGTCAAAAACGTGAAG	900
Trace	841	..... <b>A</b> .....	900
Genome	901	ATATTTGTATCCCATGTGAGTGCTCACCAATGGGTGACCTCAGCAGAGGGGGATTTTAAC	960
Trace	901	..... <b>A</b> . <b>A</b> .....	960
Genome	961	AATCAAGTGGATAGGAT	977
Trace	961	.....	977

**A DNA editing candidate at the locus of a human retrotransposon.** TI#1735626615 aligns uniquely to Chr2 where the known retrotransposon HERVL-A1 is located. A cluster of mismatches (worst mismatch phred 35; best mismatch phred 49) suggests that the trace originates from an edited version of the element. GG-to-AG (11/15) and GA-to-AA (4/15) motifs suggest the preferred dinucleotide context for APOBEC3G and APOBEC3F.

X. <i>T</i> Genome	ATCAGTCTGCTGCTTTTTTAGGAGTTTAAAGGACAAGTAAAGCCTCAGTCAGTGGGAGGGT	
1810455972	.....ggg.....g.....g.....	234
1810477902	.....g.....g.....	334
1065483469	.....ggg.....	283
1065490247	.....ggg.....	328
1065466398	.....ggg.....	524
1065471353	.....g.....	535
1669879253	.....g.....g.....	464

X. <i>T</i> Genome	TGGGCCTCCACCATTTTCCCTACAGCCTCCCAGGTATCCCCAGTGCCGTAGTCAGGAAAA	
1810455972	.....g.g.....g.....	294
1810477902	.....g.....	394
1065483469	.....g.g.....g.....g.....	343
1065490247	.....g.....g.....	388
1065466398	.....g.g.....g.....g.....	584
1065471353	.....g.....g.....	595
1669879253	.....g.....	524

X. <i>T</i> Genome	CACCAAGTCGGACTAAGGCAGAGGGTATACTTGGGAGGCCGGGGTAAGATGGCAGAGGCG	
1810455972	.....gg.....g.....g.....g.....	354
1810477902	.....gg.....g.....g.....	454
1065483469	.....gg.....g.....g.....g.....	403
1065490247	.....gg.....g.....g.....g.....	448
1065466398	.....gg.....g.....g.....g.....	644
1065471353	.....gg.g.g.....g.....g.....	655
1669879253	.....g.....g.....g.....	584



**Evidence for RNA editing in *X. Tropicalis*.** Multiple traces (of RNA origin) show numerous A-to-G mismatches. The predicted RNA structure shows a long dsRNA structure which is the preferred target of editing by ADARs.

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# **Analysis of individual genomes**

Use GeneTests to focus on genes where clinical action is already taken

Convert variants in HG18 coordinates into gene/protein coordinates

Cross-reference with OMIM to obtain a list of known variants with pointers into the literature

Obtain allele frequencies when available  
(typically not available for rare variants)

Ref. coordinate Gene, amino acid change	Genotype Ref. allele, trait-assoc'd allele <sup>1</sup>	MAF	Associated trait	Proposed clinical action	OMIM dbSNP
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<b>chr21:34664672</b> <i>KCNE2</i> , Q9E	<b>C/G</b> C G	—	<b>Acquired long QT syndrome susceptibility</b> [elderly African American female; more clinical data needed]	<b>Electrocardiogram, avoid drugs causing prolonged QT intervals</b>	<b>603796.0001</b> —
<b>chrX:38111547</b> <i>OTC</i> , K46R	<b>G</b> A G	0.441	<b>Ornithine transcarbamylase polymorphism</b> ; apparently benign and not known to be associated with OTC deficiency	<b>None</b>	<b>300461.0009</b> rs1800321

<sup>1</sup> All DNA sequences are given for the NCBI reference sequence + strand; where possible, the reference allele is listed first in heterozygous genotypes.

**Analysis of an individual African genome reveals a rare mutation—KCNE2 Q9E—not present in dbSNP. Since the individual is anonymous, recommendations cannot be returned to them.**

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aggaggggaagcatgtctactttatccaatttcacaG
aggaggggaagcatgtctactttatccaatttcacaC
ggaggggaagcatgtctactttatccaatttcacaCa
aggggaagcatgtctactttatccaatttcacaGaga
gggaagcatgtctactttatccaatttcagaGagac
gggaagcatgtctactttatccaatttcacaGagac
ggaagcatgtctactttatccaatttcacaGagacg
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atgtcttctttatccaatttcacaGagacgctggaa
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tcacaGagacgctggcagacgtcttcggaaggatt

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\*

C 25 sum(q)=676

G 22 sum(q)=607

T 2 sum(q)=10

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The Free Factories infrastructure was used to assemble the raw reads—120 gigabases—from HapMap NA18507. The alignment for KCNE2 Q9E is shown above. SNPs for this genome did not accompany Bentley et al. (2008) Nature.

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# PersonalGenomes.org

Subject & public access (not just research elite)

Entrance exam to ensure highly informed consent

**Scalable to millions of research subjects,  
budget \$1,000/person for DNA & trait data**

Highly integrated, holistic, systems-biology

Cells available for personal functional genomics

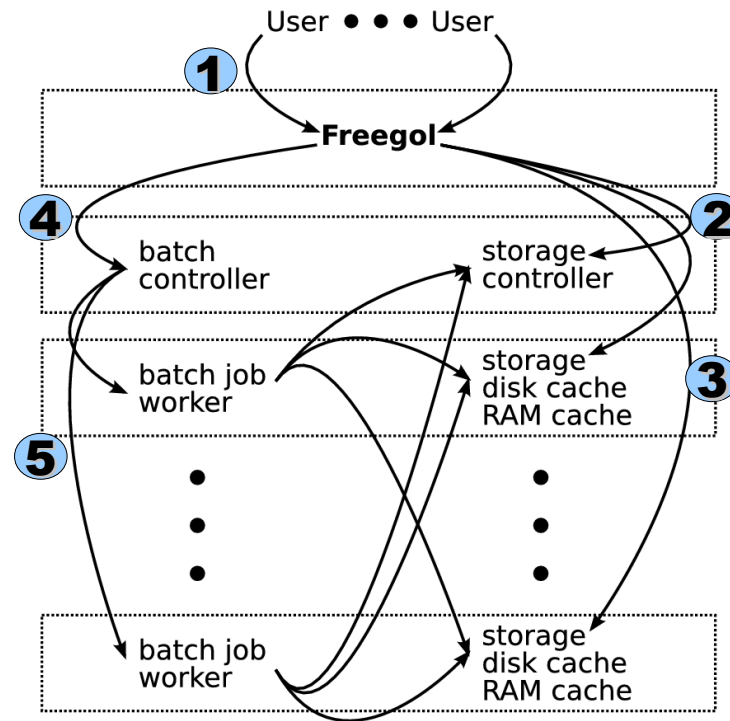


How do we organize  
computational resources to  
serve the combined needs of  
scientists, physicians and the  
general public?

The diagram illustrates the network architecture of the Free Factory. It shows four external groups (Public, Scientists, Physicians) on both the left and right sides, connected to a central network. The central network consists of four 'Freegols' (represented by boxes with numbers 12, 12, 48, and 48) and a central '48 node cluster'. A 'VPN' (Virtual Private Network) is shown as a star shape connecting the four Freegols. The top two Freegols (12) are connected to 'data acquisition instrument' boxes, which are in turn connected to 'administrators' (represented by three stick figures). The bottom two Freegols (48) are connected to the '48 node cluster'. The entire network is labeled 'Free Factory' at the top.

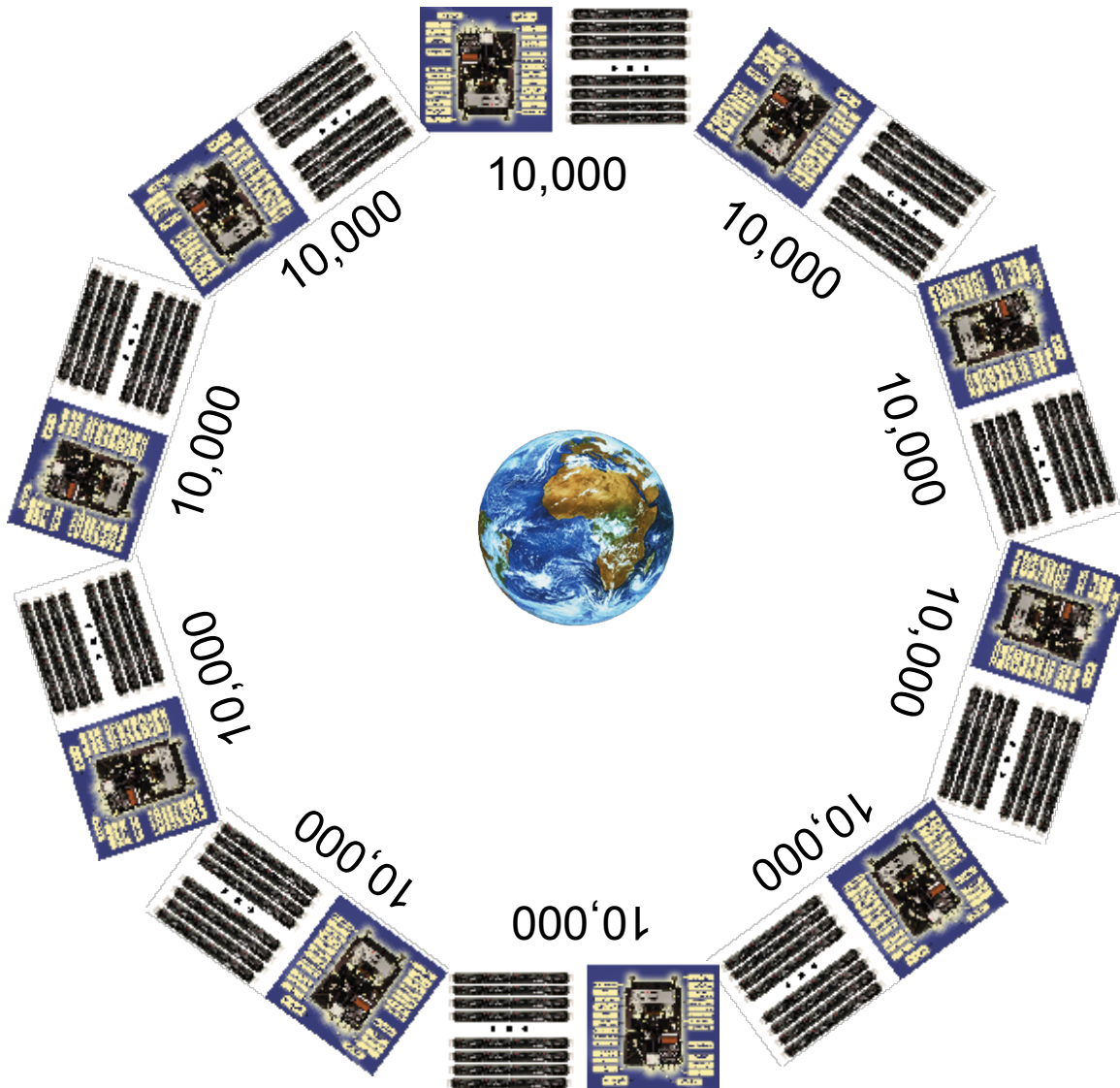
## A shared infrastructure for web service virtual machines, which I call “Freegols”.

**Freeegols—or Free Golems (another word for robot)—operate in independent virtual machines running on the Free Factories infrastructure.**



**As a Freeegol services many simultaneous user requests, it continually supervises “workflows” that process terabytes of data and consume many thousands of CPU hours**

# Scalable Infrastructure for 100,000 people



Maintain infrastructure close to participants

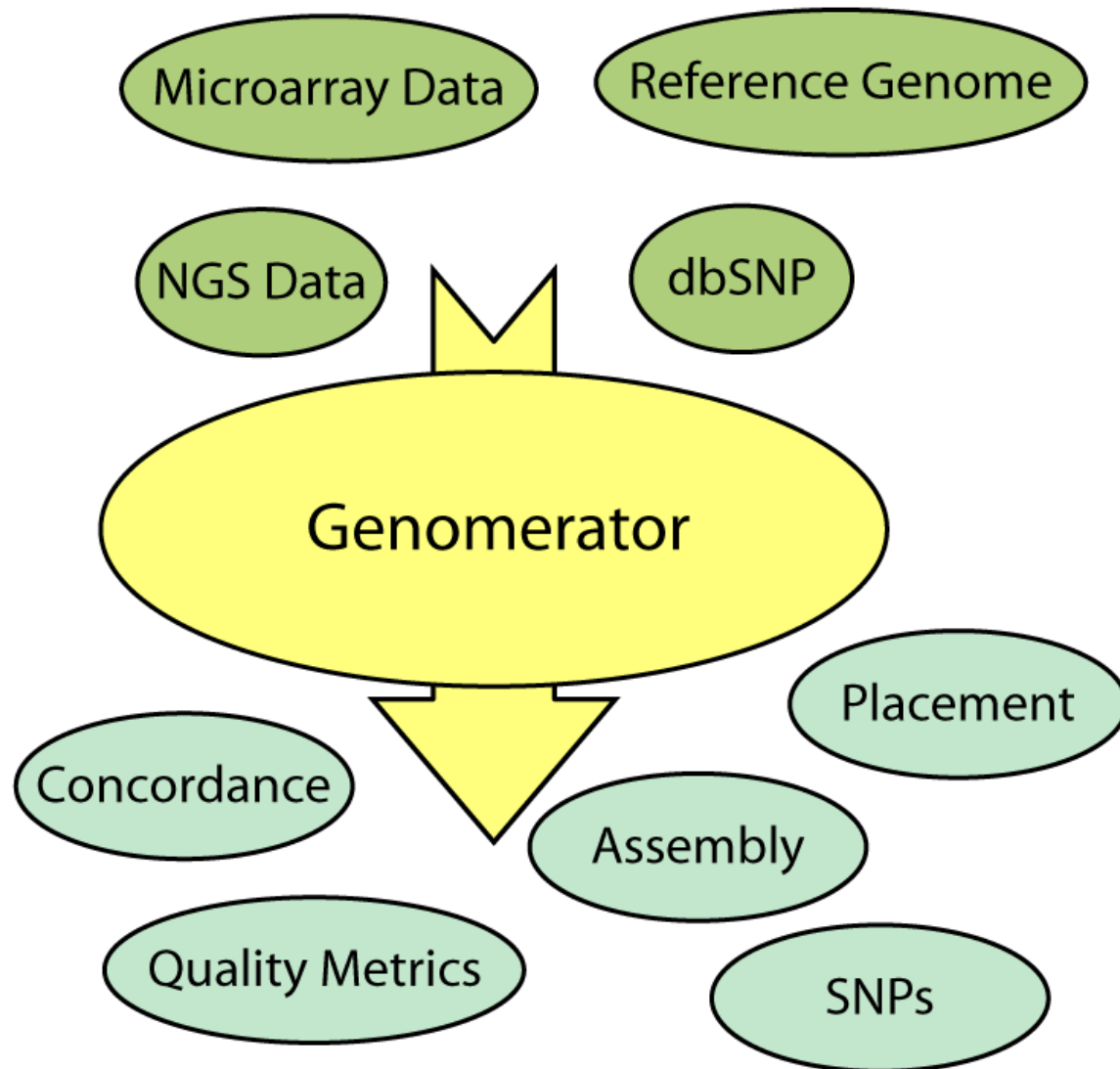
Add sequencing instruments, computational clusters, and storage independently

Freegols can use storage and compute resources from any Free Factory

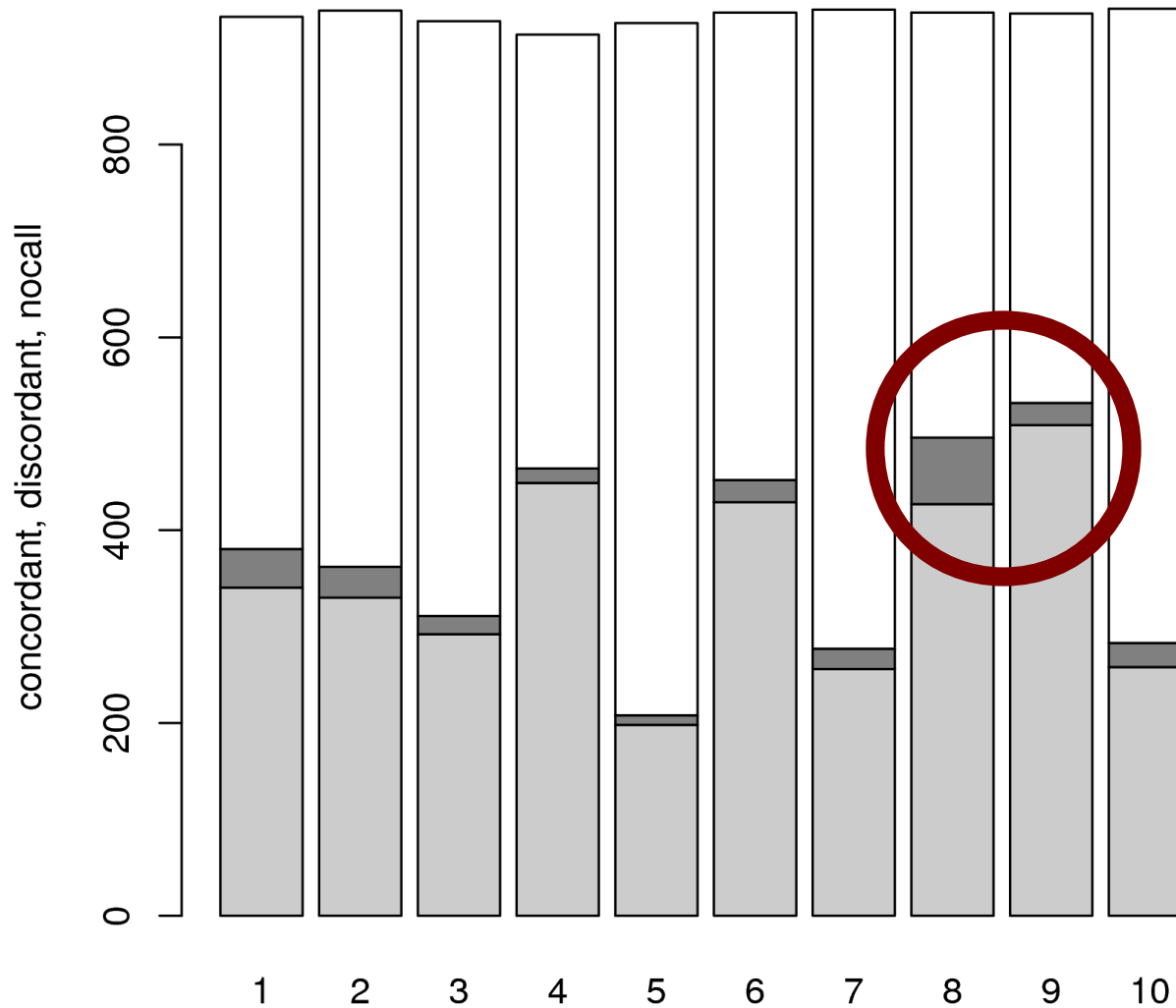
Fault-tolerant to hardware and software failures

Built-in provenance tracking

# Genomerator manages Next-Generation-Sequencing data, launches workflows, and, generates quality metrics

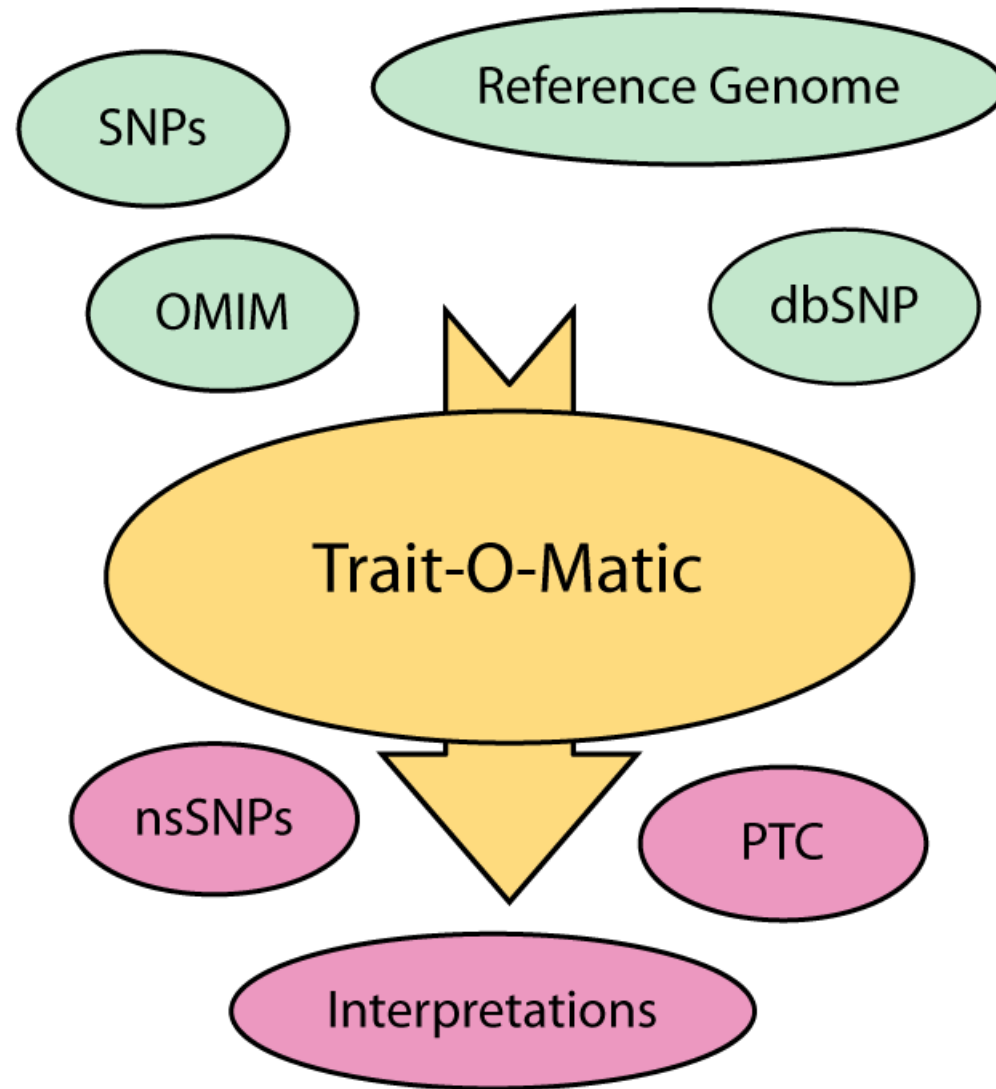


**Concordance with Affy (2s3c)**

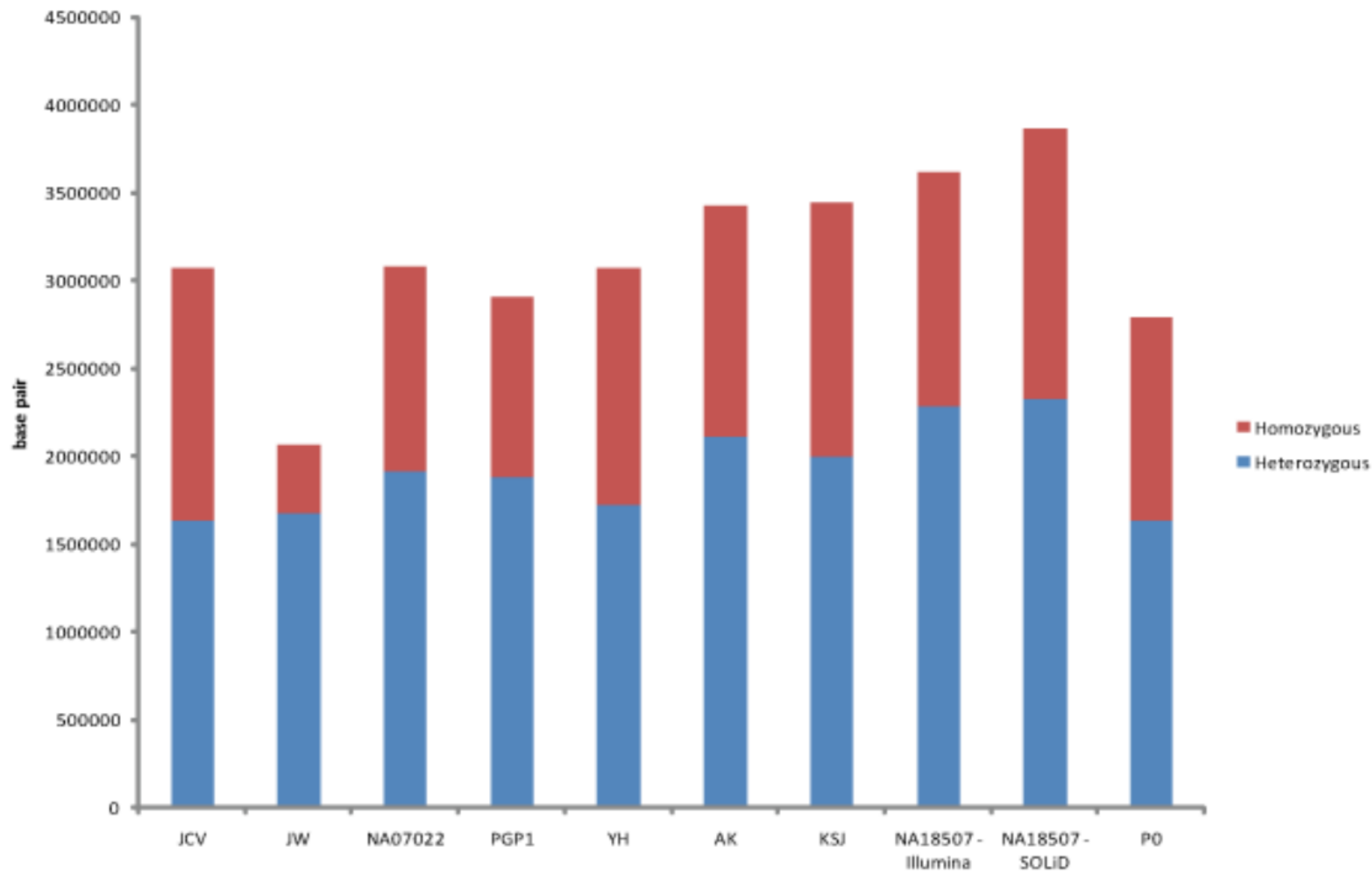


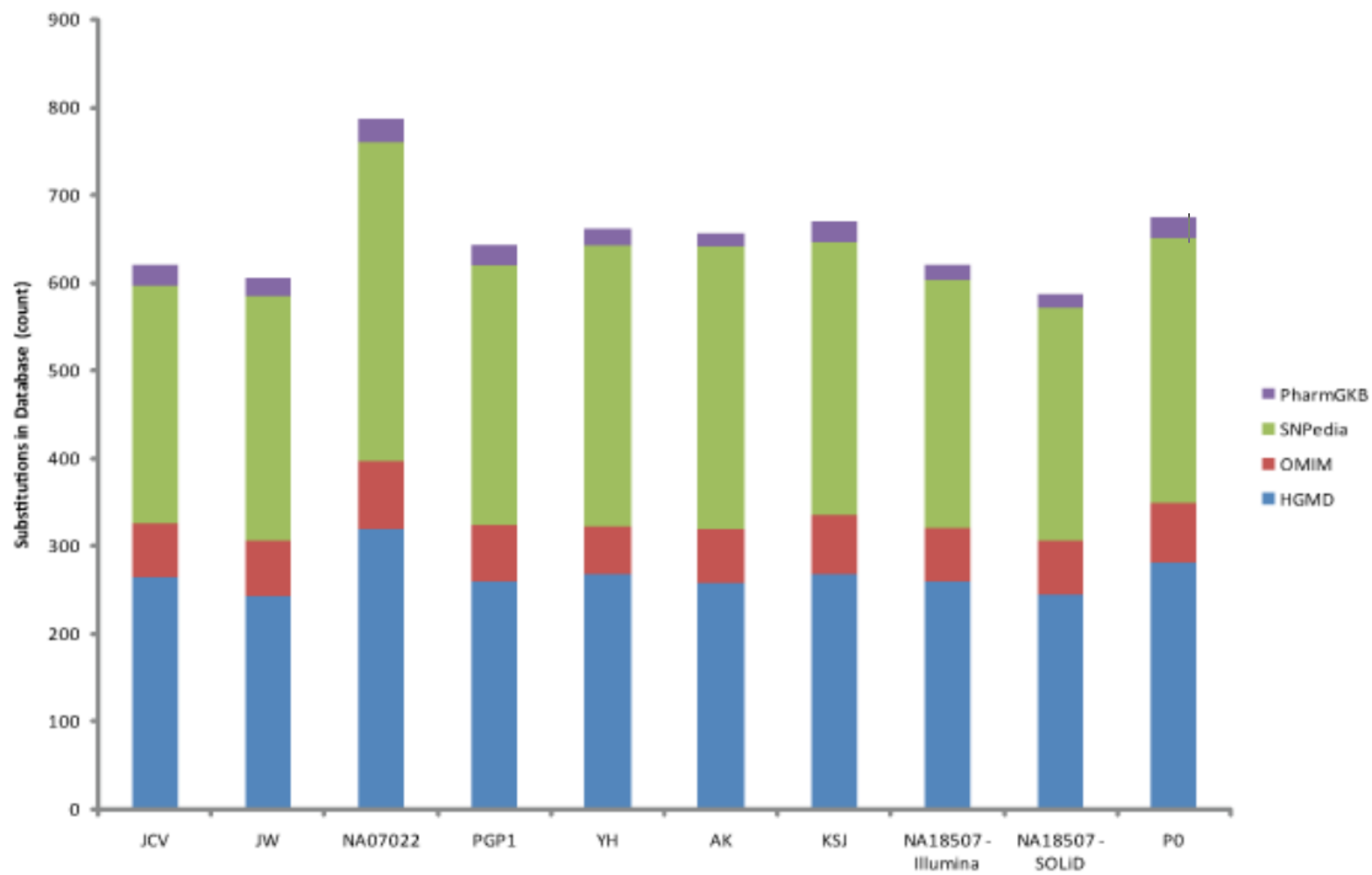
**By reprocessing the data, from images, we can improve the accuracy of PGP8 (the worst sample) to be equivalent to PGP9 (the best) while increasing the number of called variants.**

# Trait-o-matic interprets variants



## All Substitutions

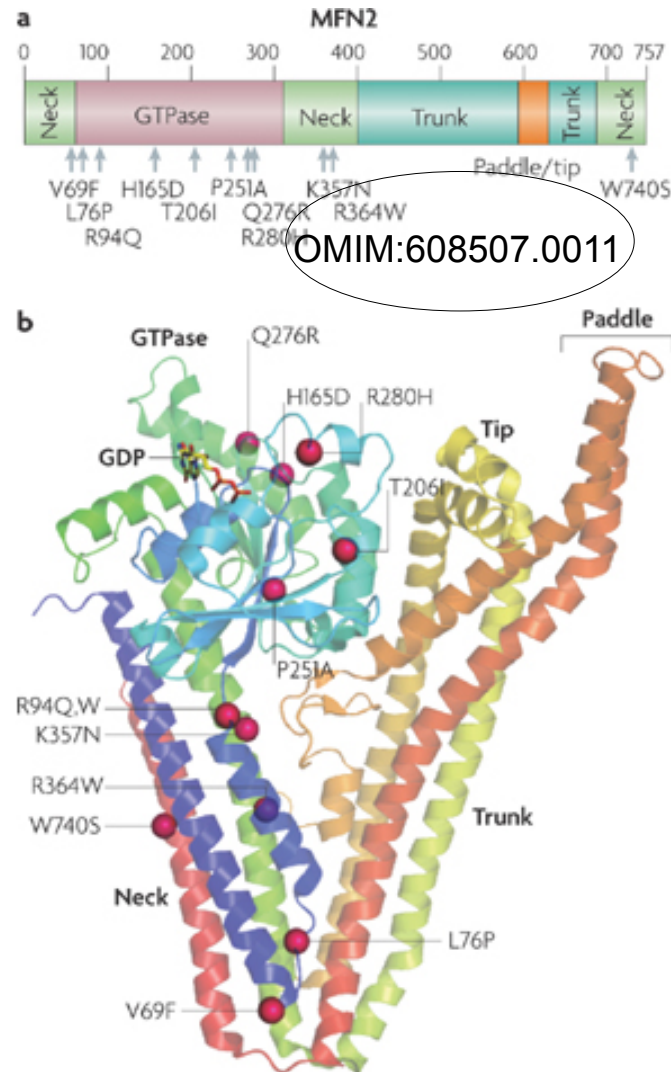




# Trait-o-matic cross-references variants with major databases and looks for damaging coding changes

PGP2 – MFN2 R364W –  
HEREDITARY  
MOTOR AND SENSORY  
NEUROPATHY VI

?



PGP1 – GHR G186\* –  
(associated with)  
INCREASED  
RESPONSIVENESS TO  
GROWTH HORMONE

?

6'4"



## PGP1 HGR Mutation

chr5	42735769	42735805	GAAGCACACGcAaTGCAGATaTTcaGAAaGGAtGG
chr5	42735776	42735812	CaCgcAATgCaGaTaTtCagaaA <b>t</b> gATggAtggttc
chr5	42735776	42735812	CacGCaaTGCaGatATTcaGaaA <b>T</b> GaTggATggtTc
chr5	42735776	42735812	CAcGCAATGCAGaTaTTcagaAA <b>T</b> gatggatggtTc
chr5	42735776	42735812	CACGCAATGCAGATATT <b>C</b> AGAA <b>A</b> TGATGgATGGtTc
chr5	42735790	42735826	ATTcAGAAAGGATGGATGGTTcTGGAGTATGAAC <b>T</b> T
chr5	42735790	42735826	AttcAgAAAGGATGGATGGTtCtGGAGTATGAAC <b>t</b> T

★

## PGP2 MFN2 Mutation

chr1	11984646	11984682	AGTGAAGACCAAGTTT <b>G</b> AGCAGCACACGGTCCGGGC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACACGGTCCGGGCCAAGCAGATTGC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACAcGGTCCGGGCCcAAGCaGATTGC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACACGGTCCGGGCCAAGCAGATTGC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACACGGTCCGGGCCAAGCAGATTGC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACACGGTCCGGGCCAAGCaGATTGC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACACgGTCCgGGCCaaGCAGATTgC
chr1	11984658	11984694	GTTT <b>G</b> AGCAGCACACGGTCCGGGCCAAGCAGATTGC
chr1	11984662	11984698	GAGCAGCACACGGTCCGGGCCAAGCAGATTGCAGAG
chr1	11984662	11984698	GAGCAGCACACGGTCCGGGgCCAagCAgATTgCAGAg
chr1	11984662	11984698	GAGCAGCACACGGTCCGGGCCAAGCAGaTTGCAGAg
chr1	11984662	11984698	gAgCAGCACACgGTCCGGGCCaAGCAGATTGCAGAG
chr1	11984665	11984701	CAGCACACGGTCCGGGCCAAGCAGATTGCAGAGGCG
chr1	11984667	11984703	GCACACGGT <b>C</b> TGGGCCAAGCAGATTGCAGAGGCGGg
chr1	11984667	11984703	GCACACGGT <b>C</b> TGGGCCAaGCAGATTGCAGAGGCGGg
chr1	11984667	11984703	GCACACGGT <b>C</b> TGGGCCAAGCAGATTGCAGAGGCGGg
chr1	11984667	11984703	GCACACGGT <b>C</b> TGGGCCAAGCAGATTGCAGAGGCGGt
chr1	11984668	11984704	CACACGGTCCGGGCCAAGCAGATTGCAGAGGCGGTT
chr1	11984668	11984704	CACACGGTCCGGGCCAAGCAGATTGCAGAGGCGGTT

★

**So what went wrong? The error probably occurs in an amplification step required by the capture process.**

# Trait-o-matic finds MYL2 A13T in PGP6

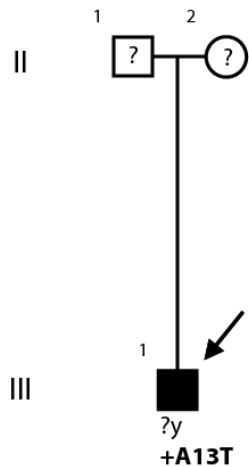
OMIM:160781.0001

PGP6 –MYL2 A13T–  
CARDIOMYOPATHY,  
HYPERTROPHIC,  
MID-LEFT VENTRICULAR  
CHAMBER TYPE, 2

?

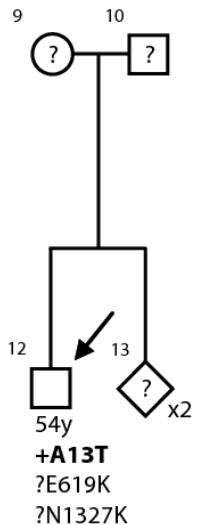
Poetter et al., 1996

PGP6

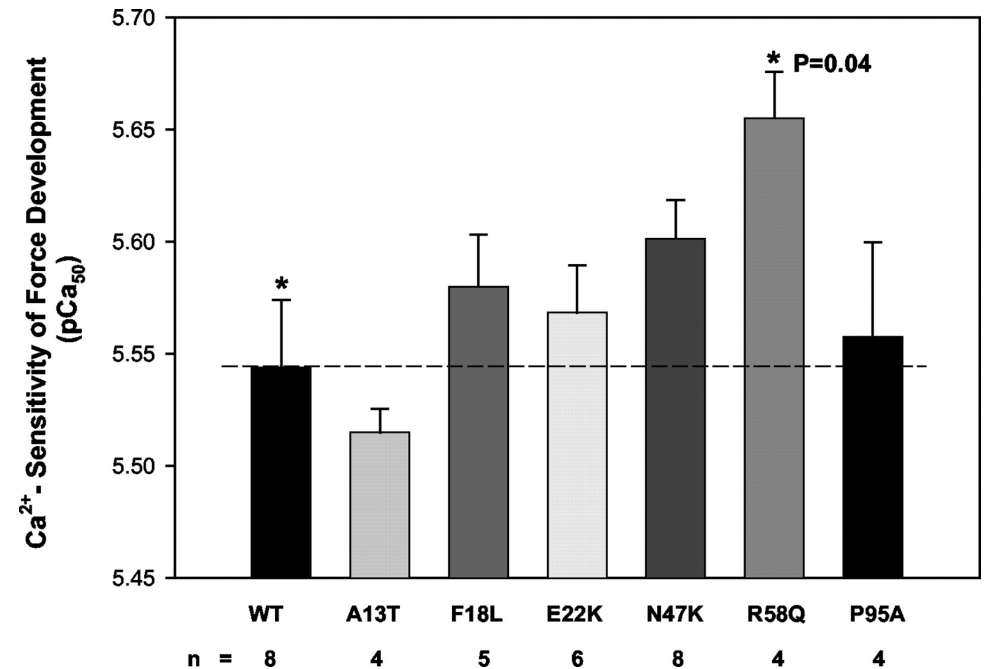
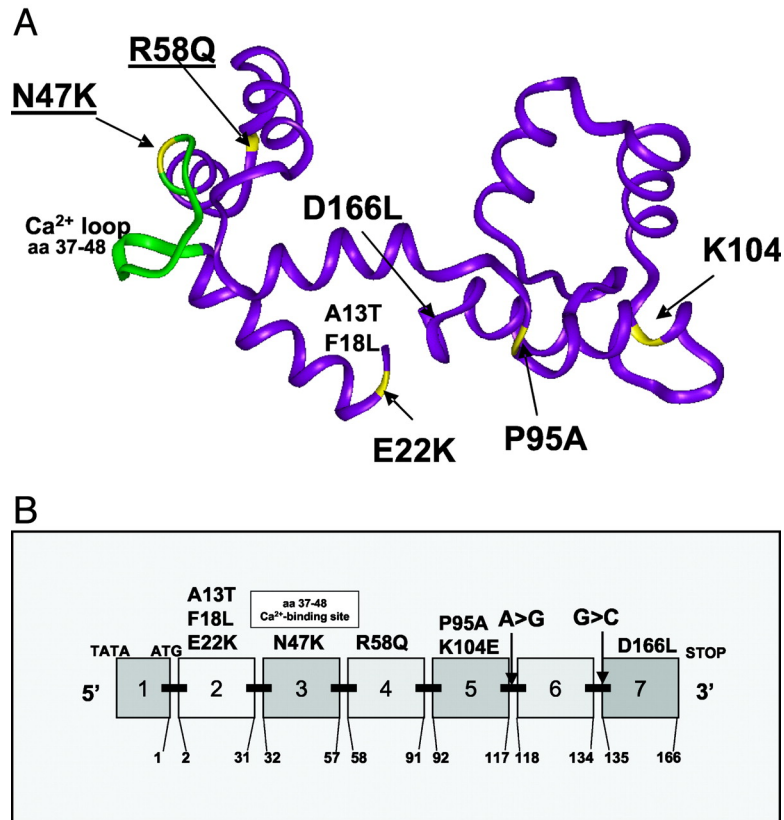


Ventricular  
RLC  
Human  
Pig  
Mouse  
Rat  
Consensus

	10	20	30	40	50	60
Human	MAPKKAKKRAGGANSNVFSMF	EQTQIQEFKEAFTIMDQNRDGFIDKNDLRDTFAALGRVN				
Pig	MSPKKAKKRADGANSNVFSMF	EQTQIQEFKEAFTIMDQNRDGFIDKNDLRDTFAALGRVN				
Mouse	MAPLFAKKRIEGGTSNVFSMF	EQTQIQEFKEAFTIMDQNRDGFIDKNDLRDTFAALGRVN				
Rat	MSPKKAKKRLEGGSSNVFSMF	EQTQIQEFKEAFTIMDQNRDGFIDKNDLRDTFAALGRVN				
Consensus	MaPkkAKKRaeG-nSNVFSMF	EQTQIQEFKEAFTIMDQNRDGFIDKNDLRDTFAALGRVN				



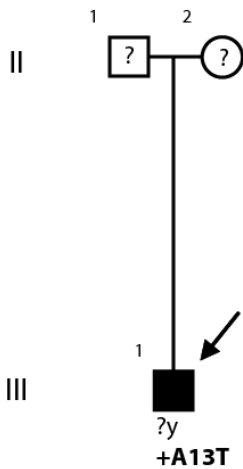
# Effect of MYL2 A13T is inconclusive in functional studies



# More clinical data for MYL2 A13T

I

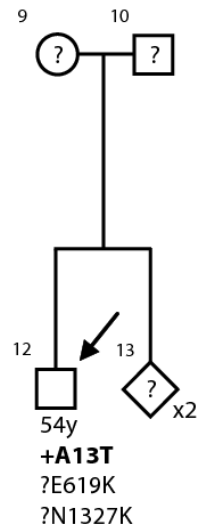
Poetter et al., 1996



III

IV

PGP6



**Free Factories can  
help scientists,  
physicians and the  
general public work  
together to advance  
personalized  
medicine**

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